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FDA-approved drug labeling for the study of drug-induced liver injury☆

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Drug-induced liver injury (DILI) is a leading cause of drugs failing during clinical trials and being withdrawn from the market. Comparative analysis of drugs based on their DILI potential is an effective approach to discover key DILI mechanisms and risk factors. However, assessing the DILI potential of a drug is a challenge with no existing consensus methods. We proposed a systematic classification scheme using FDA-approved drug labeling to assess the DILI potential of drugs, which yielded a benchmark dataset with 287 drugs representing a wide range of therapeutic categories and daily dosage amounts. The method is transparent and reproducible with a potential to serve as a common practice to study the DILI of marketed drugs for supporting drug discovery and biomarker development.

Introduction

Many drugs have either been discontinued from clinical trials or withdrawn from the market after being approved because of hepatic adverse effects [1,2]. Some of these adverse events can be serious in nature as evidenced by drug-induced liver injury (DILI) being listed as the leading cause of acute liver failure in the USA [3]. Thus, DILI has become one of the most important concerns in the drug development and approval process [4,5]. DILI has also been identified by the FDA Regulatory Science Initiatives as a key area of focus in a concerted effort to broaden the agency's knowledge for the better evaluation of tools and safety biomarkers (http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm228131.htm).

Some drugs are more likely to cause hepatotoxicity or liver injury than others, and severe DILI is of most concern. Recently, the FDA has published guidelines for assessing the potential for a drug to cause severe DILI in premarketing clinical evaluation [6]. The toxicological community has made great efforts in developing biomarkers and methodologies to assess hepatotoxicity, including DILI beyond classical animal testing, for all chemicals. The representative methods include, but are not limited to, QSAR assessments [7], *in vitro* assays [8], high-content screening assays [9] and 'omics' studies [10]. Some of these approaches are being evaluated by large government-initiated efforts for developing alternative methodologies for toxicity assessment, such as Tox21 [11] and ToxCast [12] in the USA, and the REACH program [13] in Europe. All of these efforts require a list of drugs with well-annotated DILI potential to guide the methodology development and assess their performance characteristics (i.e. sensitivity and specificity) [14].

A drug classification scheme is essential to facilitate the community-wide effort to evaluate the performance characteristics of existing DILI biomarkers and discover novel DILI biomarkers. However, there is no commonly adopted practice by which the research community can classify a drug's DILI potential in humans. Our study focused on using FDA-approved drug labels to develop a systematic and objective classification scheme for categorizing the DILI potential of a drug. This approach can be used for retrospective analysis of drugs to support studies to identify DILI biomarkers using emerging molecular technologies, thus improving drug safety and development.

Drug labeling

The assessment of hepatotoxic risk associated with individual drugs is a challenge [15]. Three attributes of a drug are important

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1359-6446/06/$ - see front matter. Published by Elsevier B.V. doi:10.1016/j.drudis.2011.05.007

for its DILI assessment: (i) causality – is liver injury caused by a drug or other causes? (ii) incidence – how many cases are deemed significant? and (iii) severity – how severe an injury is considered as a clinically relevant DILI [e.g. elevated alanine transaminase (ALT), Hy's law, disability and hospitalization, liver failure, liver transplantation or death]? The question is: how should these three sets of evidence be balanced to achieve an objective and reproducible way to assess the DILI potential of drugs?

There have been several attempts to classify drugs according to their DILI potential [9,16–24]. Most apply predefined criteria to the DILI cases from the literature, such as the number of case reports [9,16]. To assess correctly hepatotoxic risk based on case reports, reliable figures on the incidence of hepatic injury among recipients of drugs and accurate definitions of the characteristics and severity of the injury are necessary [25]. However, exact figures on the incidence of hepatic injury are unavailable primarily because of the serious under-reporting of adverse events [26,27], which makes the accuracy and reproducibility of this approach extremely difficult, if not impossible [16]. Consensus based on histopathological findings from pathologists [28,29] is another approach. However, not every patient with hepatic injury is biopsied and prominent experts do not always agree on the likelihood that a drug caused the injury. Thus, consistent assessment based on expert consensus, although possibly better in quality, is limited to data regarding small sets of drugs and incidents.

FDA-approved drug labels contain a wealth of information about adverse drug reactions from clinical trials and post-marketing surveillance. Drug labeling is regulated by law under the Code of Federal Regulation (CFR) Title 21 (Food and Drugs) Part 201 (Labeling), known as 21CFR201.56 (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=201.57). The FDA also provides guidance for preparing the labels [30–32]. The information included in the labels is agreed upon by regulatory, industry and consulting experts who have incorporated their contributions over decades, reflecting the best thinking at the time [33]. Thus, the drug labeling implicitly balances the information of causality, incidence and severity based on (i) data from controlled trials, (ii) published literature reports and (iii) spontaneous reports to AERS (adverse event reporting systems) [31,34]. The labels are also updated because new data are produced for individual drugs. FDA drug labeling also provides safety information for every approved drug, whereas studies based on case reports or expert consensus are usually limited to a subset of marketed drugs. Thus, it is generally considered that, although not perfect, drug labeling contains the best and most consistent information; probably better than literature reviews for drugs that, particularly, have been on the market for long periods of time [33].

In this study, we focused on FDA-approved labels for prescription drugs to assess the hepatotoxic risk associated with the ever-increasing number of marketed drugs and to develop a classification to support perspective studies for drug development and risk assessment. Several sources can be used to retrieve drug label information. Most of the previous articles have used the Physician's Desk Reference (PDR) [18,35–37]. We used DailyMed (http://dailymed.nlm.nih.gov/dailymed/about.cfm) instead of the PDR because of three reasons: (i) DailyMed inventories more labels than the PDR; (ii) DailyMed is in the public domain and is freely accessible, whereas the PDR is a commercial source; and (iii) DailyMed drug labels are updated daily, whereas the PDR is updated annually.

The prescription drug labels were designed by the FDA in 1979 [38] and then revised in 2006 to include more-comprehensive information [39]. This revised version contains 17 different sections, including a highlighted section briefly summarizing the most important information. In particular, our approach to classify the DILI potential of drugs was based on three sections, namely 'boxed warning' (commonly known as black box warning), 'warnings and precautions' (warnings and precautions are separate sections in older labels) and 'adverse reactions' – denoted as BW, WP and AR, respectively hereafter.

Using drug labeling to classify the DILI potential of drugs

The overall classification scheme to assess the potential of drugs to cause DILI is presented in Fig. 1 and explained in the following three subsections.

Grouping drugs based on labeling sections

We developed a set of keywords commonly used in the labels for DILI (Fig. 1). The keywords divided drugs into four lists. Three of the lists contained drugs with at least one of these keywords present in their respective labeling section (i.e. BW, WP and AR). If a drug with keywords was found in multiple sections, it was considered to be in the section: BW > WP > AR. The remaining drugs with none of the keywords present in any of the labels were placed in the 'no match' list. The labels associated with all the lists were subsequently reviewed by manually reading the full text of the labels to ensure that the context of the DILI keywords was considered. Drugs that have been on the market for a minimum of ten years were chosen for review, as described in more detail below. The results are summarized in the Supplementary Information.

Although the text mining approach was beneficial for reducing labor as well as minimizing human error (thus enhancing the reproducibility), the DILI annotation required manual reading of the full text of the labels because different writing styles and word choices in drug labels prepared by different manufacturers made it difficult to create accurate DILI annotations by using text mining alone. More importantly, the meanings of sentences with DILI keywords could be drastically different. For example, we found that many DILI-associated warnings were associated with the pre-existing condition of liver injury (i.e. they emphasized that caution should be taken when administering a drug capable of causing liver injury specifically to patients with pre-existing liver disease) [40]. However, this does not necessarily imply that the drug will cause DILI to healthy individuals or patients with different diseases. Additionally, whether patients with pre-existing liver injury are at increased DILI risk is still debatable; some hepatologists believe that patients with an underlying liver injury are not inherently more susceptible to DILI [16]. Therefore, the presence of DILI keywords in conjunction with these types of pre-existing conditions was not considered as a DILI signal.

Determination of DILI severity

We noticed that the description of DILI severity in the labeling language varies for the drugs in the same labeling section. Because the severity of DILI has a tremendous significance in the decision

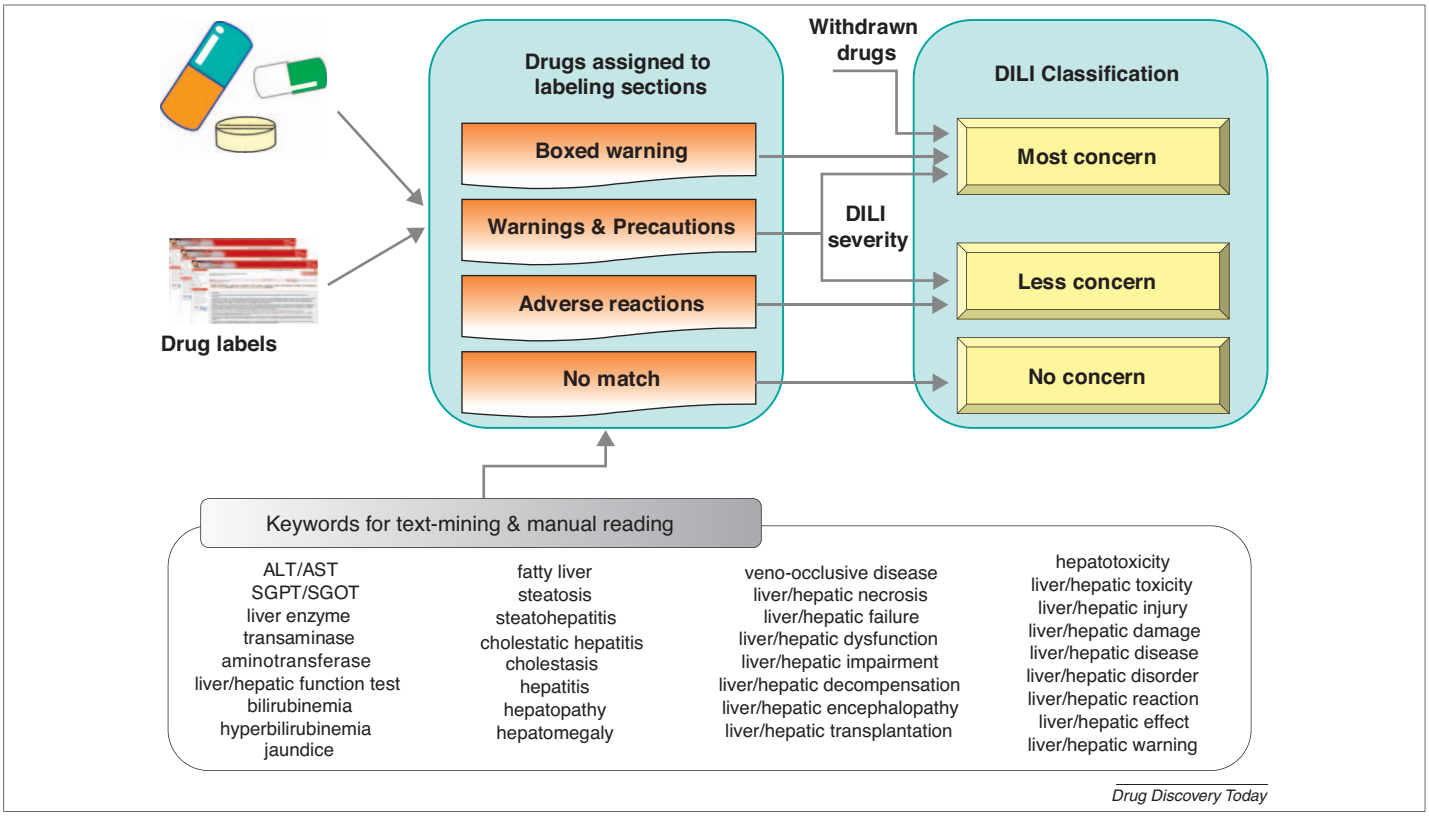

FIGURE 1

Flowchart illustrating strategies for classifying the DILI potential of drugs based on FDA-approved drug labels.

making for clinical application and the review process, we developed an 8-level system (Table 1) to assign the DILI severity for each drug after it was put into its corresponding labeling section (i.e. BW, WP and AR). To simplify the classification scheme, we grouped the 8-level system into three categories: severe DILI containing levels 6, 7 and 8; moderate DILI containing levels 4 and 5; and mild DILI containing levels 1, 2 and 3. As shown in Fig. 2, >80% of the BW drugs belong to severe DILI, whereas only 35% WP drugs and 15% AR drugs belong to the severe DILI category. According to the definition provided in 21CFR201.57, there was a hierarchical difference between the three sections; the degree of adverse effects was recorded in descending order of importance [41] with BW > WP > AR. Our analysis confirmed the hierarchical nature of these three labeling sections in reflecting relative hepatotoxic risk associated with the drugs.

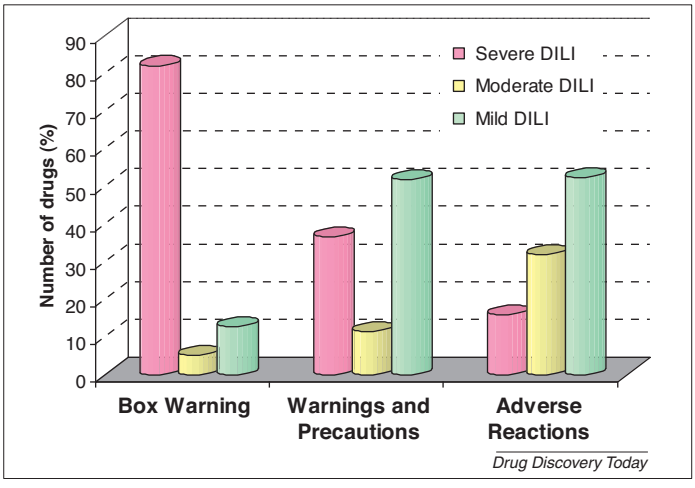

FIGURE 2

Distribution of DILI severity associated with benchmark drugs in the labeling section of boxed warning, warnings and precautions and adverse reactions.

Determination of DILI potential

DILI is a complex issue and is referred to in different contexts depending on the question raised. For example, liver injury associated with mild elevations in liver chemistry tests is treated differently for pre-approved and approved drugs. In this study, we focused on the approved drugs for which severe liver injury is more of a concern [6]. Consequently, two conditions for DILI drugs should be that (i) the causality is relatively established (not just 'associated with' or 'related to') and (ii) the liver injury is severe. Consequently, a two-step approach, as illustrated in Fig. 1, was developed to determine the DILI potential of a drug based first on which labeling section (i.e. BW, WP and AR) was affected and second on how severe (i.e. severe, moderate and mild DILI using the 8-level system) the DILI was observed for the drug in question. The factor of incidence was implicitly embedded in this process. Specifically, we considered that a severe DILI event mentioned in the label justifies the significance of events accounted for in clinical practice. This is also supported by the general understanding that, although severe DILI is a rare event, the occurrence of even a small number of cases is sufficient to raise safety concerns [34]. Using this approach, we grouped the drugs into three categories: drugs of most, less and no DILI concern.

TABLE 1

DILI severity categories based on the DILI descriptions in the drug labeling

Severity level	DILI category	Specification and keywords	Examples of labeling language
8	Fatal hepatotoxicity	Death; fatal liver failure; or needed liver transplantation	When used orally, ketoconazole has been associated with hepatic toxicity, including some fatalities
7	Acute liver failure	Liver/hepatic failure; fulminant hepatic necrosis	Elevations of liver aminotransferases (ALT, AST) and liver failure have been reported with Tracleer®
6	Liver necrosis	Histologically confirmed liver necrosis caused by drug	Rare instances of severe liver injury, including hepatic necrosis, have been reported in association with mexiletine treatment
5	Jaundice	Jaundice (clinically apparent), if caused by drug-induced hepatocellular injury	There is a low incidence of altered liver function or jaundice in patients treated with Marplan®
4	Hyperbilirubinemia	Hyperbilirubinemia without visible jaundice, if not due to other causes like Gilbert syndrome or cholestasis	Ticlopidine therapy has been associated with elevations of alkaline phosphatase, bilirubin, and transaminases, which generally occurred within one to four months of therapy initiation
3	Liver aminotransferases increase	Liver aminotransferases increase (e.g. ALT, AST, transaminase, aminotransferase); abnormal liver/hepatic function test; liver/hepatic injury	Persistent increases (to more than three times the upper limit of normal) in serum transaminases have occurred in ~1% of patients who received simvastatin in clinical studies
2	Cholestasis; steatohepatitis	Steatohepatitis, if probably caused by the drug; cholestasis, cholestatic hepatitis if caused by the drug; liver/hepatic damage/disorder/impairment/toxicity/reaction/hepatitis; hepatopathy	Jaundice of the cholestatic type of hepatitis or liver damage has been reported (in patients receiving trifluoperazine)
1	Steatosis	Steatosis; fatty liver; liver/hepatic steatosis	Lactic acidosis and severe hepatomegaly with steatosis have been reported with the use of nucleoside analogs including zidovudine

BW has been defined by 21CFR201.57 as 'certain contraindications or serious warnings, particularly those that may lead to death or serious injury'. It is the strongest medication-related safety warning that the FDA can issue for a prescription drug [42], and such a decision issued by the FDA has serious implications for the licensed practitioner, the pharmacist, the patient, the pharmaceutical manufacturer and the distributor [41]. Thus, it was justified to classify the drugs with a BW label for DILI into the drugs of most DILI concern category. We also included drugs that were withdrawn or discontinued owing to hepatotoxicity in this category.

WP is considered less severe than BW. According to 21CFR201.57, 'the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug'. Although the causal association was required, the law did not define 'the clinically significant hazard'. In the FDA's guidance on DILI [6], it was pointed out that the drugs that have a benign transient increase in ALT without any hepatotoxicity (such as aspirin, heparin, ibuprofen and statins) should be distinguished from drugs that have serious hepatotoxicity. In other words, the clinically significant DILI mentioned in the WP section should be more severe than just elevated ALT. Accordingly, we only classified drugs in this section with severe and moderate DILI defined by the 8-level system as drugs of most concern. Those drugs with mild DILI were classified as being of less concern; about 50% of the WP drugs fell into this classification.

AR is defined by 21CFR 201.57 as 'only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event'. Moreover, 21CFR201.57 further indicates that, 'This section must list the Adverse Reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable', which leads to some relatively safe drugs (e.g. cimetidine) being labeled as a DILI concern. Because causality is not required and the guilty-by-association philosophy plays a part, we considered the drugs in this section as being of less concern for their potential to induce DILI.

Annotating a drug for no association with DILI is extremely difficult. In this study, we focused on drugs that have been in the market for more than ten years to ensure the reliability and consistency of safety information in the drug labels. This ten-year criterion justified the identification of 65 drugs, 90% of which have been approved for over 25 years, to be of no DILI concern. Our approach holds the advantage when compared with the method based on the case reports for which it is impossible to define drugs of no DILI concern owing to under-reporting [26]. For example, some authors set an arbitrary threshold based on the number of case reports (such as ten reports) to separate DILI from no concern drugs to minimize the number of potential false positives in case-report-based methods [9]. However, this kind of threshold is not scientifically justified and could increase the risk of introducing false negatives. By contrast, the drug-label-based method is much more straightforward and reliable. If any DILI events were reasonably associated with drug usage, regardless of whether the causality was established or not, they were recorded in the labeling by law. Therefore, if a drug label did not mention any DILI events established over a long period of time we could reasonably consider it to be of no DILI concern.

Benchmark dataset

To serve as a benchmark dataset, we compiled a drug list that satisfied the following criteria: (i) has an FDA-approved label; (ii) for human use only; (iii) contains a single active molecule in the

dosage form; (iv) administered through oral or parenteral route; (v) approved for over ten years and (vi) commercially available and affordable for future study. These criteria were deliberately chosen based on certain rationales; for example, we only included drugs with a single active ingredient in the dosage form to establish a clear causal relationship between a drug and a liver injury. We do acknowledge that some drugs with multiple compounds have also been implicated for DILI in clinical reports [43]; however, we did not consider them because the DILI cause might be caused by more-complex reasons, such as drug–drug interaction. Another factor used to select drugs was the route of administration; because the toxic target in our study is the liver, we chose drugs that have systemic effects, such as those administered either orally or parenterally (e.g. intravenous or intramuscular injections), as opposed to drugs that have local effects, such as those administered topically, nasally and ophthalmically. Drugs having BW for DILI and drugs that were discontinued or withdrawn because of DILI in US and European markets were not subjected to the latter two criteria because of their strong association with DILI.

When we prepared this manuscript, the benchmark dataset contained 287 drugs (Supplementary Information): 137 drugs of most concern, 85 of less concern and 65 with no concern of causing DILI. The benchmark dataset represents a diverse collection of therapeutic categories and a fully covered dosage range (Fig. 3). All of the drugs in the benchmark dataset and their associated information (such as the specific DILI-related descriptions in the labels and DILI severity) collected throughout this project are organized in the HepaDB™ database (http://www.fda.gov/ScienceResearch/BioinformaticsTools/LiverToxicityKnowledgeBase/ucm226811.htm). The database provides a user-friendly interface for rapid navigation and Boolean searching, which supports searching by drug generic name, trade name, CAS registration number, chemical structure (including substructure search and similarity search), molecular formula, etc. The data can be cross-linked to other publicly available and related databases including DailyMed, commercial vendors, among others.

Other groups have proposed different criteria to assess DILI risk in humans. We identified several such relatively large datasets at the time this work was conducted. O'Brien *et al.* classified drugs into four categories according to the severity of human hepatotoxicity based on the frequency of an observed increase in ALT and other evidence [17]. Xu *et al.* proposed a two-level classification scheme that placed drugs in DILI-positive and -negative categories based on the drug label and the number of case reports [9]. Suzuki *et al.* created a drug list from DILI registries in Spain, Sweden and the USA, and labeled drugs as withdrawn owing to hepatotoxicity, acute liver failure association and DILI association [44]. Zimmerman compiled a DILI drug list based on the case reports from scientific literature [16]. We compared our benchmark dataset to these four literature datasets, which required their reorganization into DILI-positive and DILI-negative categories. We took the following actions: (i) we combined severe and moderate hepatotoxicity drugs as DILI-positive drugs, and non-toxic drugs were DILI-negative drugs for the dataset reported by O'Brien *et al.*; (ii) the reported two-level classification was retained for comparison with Xu *et al.*; and (iii) all the drugs reported by the studies of Suzuki *et al.* and Zimmerman are DILI-positive drugs so no reclassification was required.

The concordance of the drugs classified in our system as those of most concern with the DILI-positive drugs in other studies was high (all four comparisons had at least 90% concordance). Only

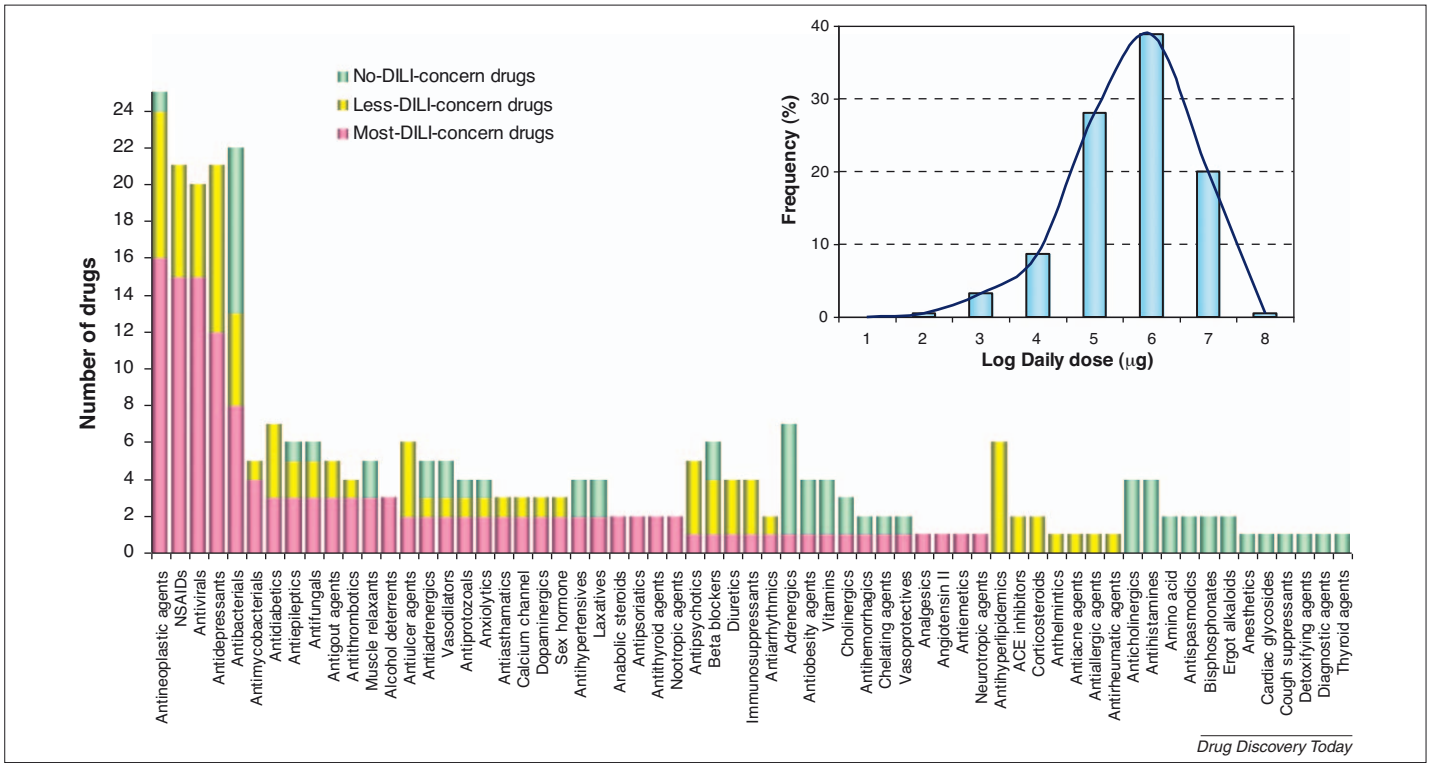

FIGURE 3

The representation of therapeutic classes of the three categories of benchmark drugs, namely drugs of most, less and no DILI concern [the small graph in the top right corner shows representation of benchmark drugs in terms of therapeutic dose (log daily dose)].

five out of 137 drugs of most concern are assigned as negatives by others; these are moxisylyte [17], carbidopa [17,9], tacrine [9], lamivudine [9] and zalcitabine [9]. These high concordances suggested that our drug-labeling-based method for the drugs of most concern was reliable. For example, 94 of the 96 drugs of most concern that overlapped with the dataset of Suzuki *et al*. have passed the causality evaluation by experts [44]. By contrast, the concordances in DILI-negative drugs of different studies compared with our 'no concern' drugs were relatively low, with 80% and 65% concordance for datasets of Xu *et al*. and O'Brien *et al*., respectively. Specifically, ten out of 65 'no concern' drugs are classified as positives by others; these are metronidazole (Zimmerman, Xu *et al*. and Suzuki *et al*.), deferoxamine (Zimmerman and Xu *et al*.), kanamycin (Zimmerman), primaquine (Zimmerman), primidone (Zimmerman), mitomycin (Zimmerman), vancomycin (Xu *et al*.), metaproterenol (Xu *et al*.), phentolamine (Xu *et al*.) and alendronate (Suzuki *et al*.) [9,16,44].

Caveats of using drug labeling

Many inherent defects are associated with drug labeling. Drafting a drug's label by the drug manufacturer is a complex process involving not only safety concerns but also efficacy, benefit:risk, legal and other considerations. The liver safety profile could therefore be worded differently for drugs with different indications, efficacy and benefit:risk ratios, despite similar hepatic risks. Because the language regarding appropriate wording and the placement of safety-related information is flexible [37], data regarding adverse effects could be disclosed using ambiguous semantic descriptions [45]. Sometimes, the mention of liver injury in the label is based on relatively little objective data and instead reflects the drug manufacturer's or the regulator's concern of the possibility of DILI. In some cases, liver injury is mentioned in the label to increase physician awareness of the potential risk, because hepatic events were reported in patients taking a related drug and there is concern that they might represent a class effect. For example, lamivudine was issued a BW because it is a synthetic nucleoside analog. It belongs to a subclass of antivirals and some of these have caused severe liver injury. In some cases liver injury is mentioned in the label to acknowledge that such cases were reported to the drug manufacturer or to the regulators. However, these reports do not necessarily imply a causal relationship between the drug and the hepatic event, because they might reflect hepatic events unrelated to the drug. Overall, labeling can sometimes be capricious and inconsistent. Therefore, care must be taken to interpret the labels in the right context, which is why the manual reading of labels was essential in this study with the goal of improving the accuracy of drug classification.

Drug labels provide comprehensive toxicity information for evaluating the hepatotoxic risk of a drug, but their contents are not constant; they are often revised once adverse effects are discovered after approval, especially in the first few years following marketing approval. In a study of drugs approved between 1975 and 1999, it was found that half of withdrawals occurred within two years following the introduction of the drug to the market, and 50% of label changes related to BW occurred within seven years [35]. To assure the reliability of the drug labels, we have only included drugs that have been marketed for at least ten years in the benchmark dataset, as well as some drugs withdrawn from the market owing to hepatotoxicity. This criterion ensures that significant adverse effects have had time to be discovered and incorporated in the labels, and that the DILI annotations are stable and reproducible.

Concluding remarks

Labeling is not perfect because it is an opinion-based rather than evidence-based process. Moreover, the labeling has been in existence for >40 years, and the terms used in the labels were not devised according to a scientifically justified master plan over the years and its usage has been evolving. Despite imperfections and limitations the labeling still reflects serious thought and consensus by experts and, in practice, is 'the closest that one can get to the truth regarding the scientific information known about a drug' [33]. It reflects the safety concerns of regulators and the drug manufacturer, and collects the consensus from the experts at that time. It is probably better than the literature and far better than the spontaneous reports to adverse effect monitoring systems such as AERS because few or even no causality assessments are performed there. We mitigated the inherent defects in labeling by using a classification system that involved manually reading and balancing the information from the FDA drug labels, as well as by selecting drugs with restrictive criteria. Using our classification system, we generated a drug list that can be used as a benchmark dataset for DILI research in the scientific community that will aid the evaluation of the performance characteristics of existing DILI biomarkers and the development of novel DILI biomarkers using emerging molecular technologies. The proposed approach should be equally applicable to other toxicity endpoints, such as renal toxicity.

Acknowledgements

The report study is a part of FDA's Liver Toxicity Knowledge Base (LTKB) project that is supported by the FDA's Critical Path Initiative, the Office of Women's Health and the Chief Scientist Challenge Grant. Vikrant Vijay, Qiang Shi and Zhichao Liu greatly appreciate the opportunity to work at NCTR through the ORISE program. The authors have no conflicts of interest related to this study.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.drudis.2011.05.007.

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